UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 8 Cases*	

GENERAL EXPERT REPORT OF MILES MURPHY, MD MSPH FACOG

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I. Background

I am a medical doctor licensed in the State of Pennsylvania. My education and employment history can be found in my curriculum vitae (CV) found as Attachment 1. In summary, I earned my medical degree from the University of Pittsburgh in 1997. Upon graduating, I began my four-year residency in Obstetrics and Gynecology (Ob/Gyn) at Lehigh Valley Hospital, which I completed in 2001. Following that I completed a three-year fellowship in Female Pelvic Medicine & Reconstructive Surgery (a.k.a. Urogynecology) at the University of Louisville. I completed this program in 2004, at which time I also earned a Masters of Science in Public Health (MSPH). In July of 2004, I began my practice as the Associate Medical Director of the Institute for Female Pelvic Medicine & Reconstructive Surgery, a position that I still hold. I received my board certification from the American Board of Obstetrics and Gynecology in 2006, and in 2008 I became the Director of the Division of Urogynecology at Abington Memorial Hospital and an Assistant Clinical Professor of Obstetrics and Gynecology for the School of Medicine at Temple University.

My practice is a subspecialty practice consisting entirely of women with disorders of the pelvic floor. The vast majority of patients that I treat present with urinary incontinence (UI), pelvic organ prolapse (POP), or a combination of the two. I perform 6 – 8 urogynecologic surgical cases per week and have done so for the

past 11 years (the first three years in fellowship). Approximately 3/4 of these cases are for POP and the other 1/4 are for incontinence alone. I perform both reconstructive and obliterative surgeries. I perform transvaginal and transabdominal (including robotic-assisted laparoscopy) surgery. I perform reconstructive surgery with and without mesh. I estimate that I have performed approximately 1000 surgeries utilizing the Prolift system. A list of materials that I have reviewed that are pertinent to the subject of pelvic floor disorders and this case, in particular, can be found in the attached bibliography (Attachment 2).

II. SUMMARY OF OPINIONS

Below is a summary of my opinions as set forth in greater detail in this report. All opinions below and in this report are to a reasonable degree of medical or scientific certainty, and are based upon my training, education, experience, discussions with colleagues, and review of materials and the medical and scientific literature.

- Pelvic organ prolapse is a burdensome condition to many women. There are conservative as well as surgical options for treating prolapse. Conservative options for treating prolapse may not be always be seen as a suitable option for some and when used, do not always work.
- Native tissue repairs to treat prolapse had high failure rates and the abdominal sacrocolpopexy had the potential for high morbidity as it is an invasive procedure. As a result, surgeons looked to mesh as an option to treat prolapse via the minimally-invasive vaginal approach.

- Monofilament, macroporous polypropylene was and still is the most commonly used surgical mesh to treat prolapse via both the abdominal and vaginal approach, and was an acceptable material to use in Prolift. Polypropylene has been used for decades to treat hernias, urinary incontinence, and prolapse and the mesh and Prolift have been studied in multiple trials. Prolift provides better long term stability than traditional native tissue repair surgery and the clinical study done on Prolift and the transvaginal mesh exceeds that done on other products. I have seen no evidence of mesh degradation in my clinical practice and I have seen no increased risk of infection associated with the mesh beyond that generally associated with prolapse surgery.
- All surgeries, including surgeries for pelvic organ prolapse, have potential risks. The risks for the surgical treatment of prolapse include: bleeding, blood clot formation, infection, damage to nearby structures (i.e. bowel, bladder, urethra, ureters, and in some cases the abdominal wall), formation of fistulas (abnormal connections between two organs), shortening of the vagina, difficulty emptying the bowel or bladder afterwards, difficulty controlling her bowel or bladder (i.e. fecal or urinary incontinence and urinary dysfunction), chronic pelvic and/or vaginal pain, pain with intercourse, and in very few cases, death. These risks exist regardless of whether or not a graft or mesh is used in the repair. The risk specific to the use of mesh – mesh exposure – has long been known and in the majority of cases is easily treated. Prolift, while not for ever patient and accompanied by

potential risks like every surgery, is a safe and effective treatment alternative.

- The contents of the Prolift IFU and patient brochure are adequate to warn of the potential risks of the procedure. They are not designed to replace sound surgical judgment that pelvic surgeons develop during their training and practice nor are they meant to teach the user how to perform pelvic reconstructive surgery. Nor is the patient brochure designed to replace the surgeon-patient dialogue and consenting process. The professional education program for Prolift was effective and supplemented the IFU.

III. Pelvic Organ Prolapse

"Pelvic organ prolapse" (POP) is the general term used to describe any descent or "dropping" of the female pelvic organs, such as the vaginal walls, the uterus and the organs that lay behind the vaginal walls. When the front wall of the vagina and the bladder drop, the condition is referred to as a "cystocele", when the back wall and the rectum drop, it is called a "rectocele", when the uterus drops, it is called "uterine prolapse", and when the top or apex of the vagina of someone who has previously undergone a hysterectomy, it is called "vaginal vault prolapse" or an "enterocele". Common symptoms of POP include pelvic pressure and discomfort, difficulty emptying the bowel and bladder, and conversely, in some cases, incontinence of the bowel and bladder. In many instances the pelvic organs actually protrude well beyond the vaginal opening such that there is a mass of tissue that

rubs on the patient's undergarments. These tissues can become irritated from being abnormally located outside of their normal position leading to vaginal ulceration, bleeding, and discharge.

POP is a much more common problem than many people realize. Fifteen years ago it was estimated that over 225,000 underwent surgery for correction of POP in the United States (Brown 2002). This was likely just a small fraction of the women who were actually suffering from this disorder. Another study published the same year investigating over 27,000 of women who enrolled in a clinical trial on the effects of hormone replacement therapy revealed that the rate of POP in women with a uterus was 66.1% and it was 51.2% in women who had previously undergone a hysterectomy (Hendrix 2002). This suggests that many women suffer with this condition without seeking surgical correction. There may be multiple reasons why this disparity exists; but one thing is clear, the incidence of this condition is increasing as our population ages and "baby-boomers" go deeper into their the post-menopausal years. A recent study of the prevalence of POP suggests that the number of women with symptomatic POP will increase 46% in US women between 2010 and 2050 going from 3.3 to 4.9 million women per year (Wu 2009).

The annual direct cost of pelvic organ prolapse surgery in the United States is estimated at over $1000 million dollars (Subak 2001). Evidence suggests that a fair amount of this expense can be attributed to failed primary surgery. One study showed that over a 10-year period more than 1 in 4 women will develop a recurrence of her prolapse after her initial prolapse surgery (Fialkow 2008). The average time between surgery and diagnosis of recurrence was 4.15 years and

cystocele was the most frequent element of recurrent prolapse. Among women with recurrence, 55% underwent retreatment (approximately 2/3 chose conservative management and the other 1/3 chose surgical reintervention). Another study showed that within 5 years 13% of women will undergo reoperation for failed surgery for prolapse and incontinence (Clark 2003). One additional study showed that one year after surgery, 58% of women had recurrent prolapse (defined as POPQ stage II or greater), with 10% having a prolapse 1 cm beyond the hymen (Whiteside 2004). These high rates of recurrence and subsequent consequences have driven practitioners to seek more durable techniques for repair of these complex defects.

One field gynecologic surgeons have looked to help guide these innovations is that of general surgery. The widespread use of "grafts" in abdominal hernia repair preceded that of reconstructive pelvic surgery. Grafts can be made from biologic materials (harvested from the other parts of the patient's own body, from human cadavers, or from the bodies of other species such as pigs and cows) or synthetic materials. When the synthetic materials are knitted into a screen-like configuration, they are often referred to as "meshes". The results of early randomized clinical trials of traditional (suture-based) versus synthetic mesh repairs of inguinal hernia showed superior success rates with mesh, and more recent long-term follow-up of these trials have shown a persistence of the decreased risk of recurrence with mesh repair (van Veen 2007). POP is essentially a hernia, only the organs are herniating through the pelvic floor instead of the abdominal wall. The success of mesh grafts in hernia repair spurred pelvic surgeons to adopt the same technology for POP repair.

As a result, recent surveys of professional sub-specialty urogynecology societies have shown wide-spread adoption of at least some form of graft repair by their surgeons for the treatment of pelvic floor disorders. As early as 2002, a survey of practice patterns of the International Urogynecological Association showed that more surgeons were using a synthetic midurethral sling as their procedure of choice for SUI than were using a suture-based colposuspension (Davila 2002). More recent surveys of the American Urogynecologic Society have shown that nearly half of respondents used transvaginal mesh devices for cystocele repair (Shippey 2008) and nearly all use synthetic mesh for at least some of their reconstructive procedures for SUI and/or POP (Pulliam 2007).

IV. Treatment of Pelvic Organ Prolapse

Non-Surgical Treatment Options

POP is mostly a condition that affects a patient's quality of life. It is rarely a condition that threatens a patient's life. Therefore, it is important to understand that there is usually the option of not treating POP. However, the natural history of POP is to get worse as time goes by (except in cases of transient POP that resolves within a year of pregnancy and delivery). And when POP progresses to its most advanced stages, it can have a devastating impact on a woman's quality of life; to the point where patients do not even want to leave their houses and the mere acts of standing or sitting can be extremely uncomfortable. POP negatively impacts many women's body image and self-esteem. Many sexually active women cease to be

sexually active as a result of new onset POP. Many stop exercising because of discomfort from their POP and secondary to fear of incontinence with activity. This decrease in activity can lead to weight gain which in turn can worsen the symptoms of POP creating a viscous cycle and leading to other health problems.

POP is staged on a system ranging from Stage 0 (no prolapse) to Stage IV (complete prolapse). Most women develop symptoms that are bothersome enough that they opt to seek medical care when they reach Stage II (bulging with a centimeter of the vaginal opening) (Swift 2003). At this point, most women no longer feel comfortable just living with the problem, and they desire some form of treatment. The most basic form of treatment is an exercise regimen to strengthen the muscles of the pelvic floor (a.k.a. Kegel exercises). While this can help slow the progression of POP and in cases of early stage POP can provide some symptomatic relief, it can never repair damaged connective tissue, but only strengthen the muscles around them. Furthermore, while many women know about pelvic floor muscle exercises, the majority of them either do not practice them regularly or they perform them inadequately; and the worse a woman's prolapse is the less likely she is to be able to contract these muscles with adequate strength (Moen 2009).

The other most basic form of nonsurgical treatment of POP involves the placement of a device inside the vagina that holds up the pelvic organs. These devices, known as pessaries, come in different shapes and sizes and can be fitted in the office. Some women can learn to remove and replace their own pessary, others can not. If a patient wishes this form of therapy and also wishes to engage in sexual intercourse, it is imperative that she be able to remove the device herself. Some

women find treatment with a pessary to be extremely satisfying. Other women have no interest in this type of therapy. It can result in vaginal discharge, odor, ulceration and bleeding, and most physicians want patients being treated with a pessary to be seen in the office 3-4 times per year.

A recent European study of pessary use followed a group of 246 women who chose to treat their POP with a pessary (Lone 2011). Approximately 25% of these women were unable to retain the pessary beyond 4 weeks (in other words, it kept falling out). They attempted to follow the remaining women for a period of five years, and at the end of that time period 130 (53%) of the women were still using the pessary. For those who fail, or simply do not want to even try a pessary, the main remaining option is surgical correction.

Native Tissue Repairs

Procedures for POP have been performed since the early part of the 20th Century. Different surgeons have used different techniques throughout the years, but the basic, traditional technique has involved incising the lining of the vagina in the midline and dissecting the lining off the underlying connective tissues of the vaginal walls. Once these connective tissues have been exposed they are plicated (stitched together more tightly) using absorbable sutures. Excess vaginal lining is then trimmed away from both sides of the incision and the incision is closed with absorbable suture. When this procedure is done along the front wall of the vagina it is known as an “anterior colporrhaphy” and when it is done along the back wall it is called a “posterior colporrhaphy”. When done together these procedures are often

referred to as an "A & P repair". This is often done in conjunction with a vaginal hysterectomy, when the patient suffers from uterovaginal prolapse. When the top of the vagina is prolapsing, it can also be re-suspended by suturing to various ligaments that run higher in the pelvis. Two of the most frequently used are the sacrospinous and the uterosacral ligaments.

However, multiple studies show that the connective tissues in many women with POP are weaker than the connective tissues of women who do not develop POP (Ulmsten 1987, Gilpin 1989, Norton 1992). Many signs point to a genetic predisposition to weaker connective tissues that lead to POP. Thus, these repairs using the patient's own connective tissues to correct POP (so-called "native tissue" repairs), may be destined to fail in the very women that need repair the most. These high recurrence/failure rates of native tissue repairs (Olsen 1997 & Whiteside 2004) is what has driven the need to develop more durable vaginal repairs, much the same way high failure rates led general surgeons to begin using grafts to augment hernia repairs.

Grafted Repairs

The first major attempts at using grafts/meshes to help in the repair of POP were done through a trans-abdominal approach. The procedure known as an "abdominal sacral colpopexy" (ASC) was often reserved for women with recurrent vaginal prolapse (who have already failed an attempt to correct POP using a native tissue repair), since it is a major surgery that involves operating in regions of the body not often encountered by most gynecologic surgeons. The classic technique

used in the ASC involves suturing a graft (most commonly a synthetic, monofilament polypropylene mesh) to the front and back walls of the vagina (after separating these walls from the bladder and rectum) and then suturing an extension (or tail) of the mesh up to a ligament that runs along the inner surface of the sacrum (tailbone).

ASC involves many possible risks; some of these risks are common in other gynecologic procedures but some are quite unique to ASC. As with many gynecologic surgeries it is possible to injure the lower urinary tract. And while gastrointestinal complications can occur after most gynecologic surgeries, the risk of this gastrointestinal morbidity appears to be significant after ASC (Whitehead 2007). Furthermore, unlike most gynecologic surgeries, life-threatening injury to the great vessels (common, internal, and external iliac vessels) and presacral hemorrhage is a risk with ASC (Nygaard 2004); as is infection of the sacrum itself, which can be very difficult to treat (Hart 2004, Collins 2011). Most of these complications are much more infrequent with transvaginal surgery.

Most surgeons today perform ASC using synthetic mesh grafts (Nygaard 2004), but other materials have been used in the past. In the early days of this procedure, a biologic graft was often harvested from the patient's own leg, which subjected her to the morbidity and risk of complication at the harvest site (Latini 2004). Due to the morbidity and difficulty of harvesting graft form the patient's own body, attempts were made to utilize biologic grafts from cadavers. However, many of these biologic grafts failed to provide the needed support (Kammerer-Doak 2002, Fitzgerald 2004) and, in fact, at least one RCT showed that the results with synthetic grafts were superior to biologic grafts (Culligan2005).

While ASC is still performed to this day, many gynecologists have sought ways of maximizing the benefits of ASC (i.e. the durability of a mesh-based repair) while at the same time performing the repair in the most minimally-invasive way to perform gynecologic surgery – the transvaginal approach. Prior to 2005 this generally involved incising the vagina in the same way it is incised in an A & P repair, but instead of just relying on the patient's own defective tissue to reduce the prolapse, the surgeon instead placed grafts/meshes behind the vaginal lining and attached them up to the pelvic sidewalls and/or sacrospinous ligaments. In this way, vaginal tissue did not have to be trimmed away to reduce the bulge and the repair would at least theoretically have a lower chance of recurrence because the grafts/meshes were made of durable materials.

Risks of Surgery and the "Informed Consent" Process

Sometimes advanced POP can impair defecatory or, more commonly, urinary function so severely that a patient's life can be threatened. However, this is infrequent, and therefore, as mentioned above, surgery for POP is an option that must be considered carefully in relation to other options. As with any surgery, a thorough discussion of the risks and benefits of surgery is very important. I have read Plaintiffs' experts' criticisms of the Prolift Patient Brochure. These brochures were used in my practice and I believe that they are accurate and simply tools that may be used by a surgeon. However, the Prolift Patient Brochure is not a substitute for the surgeon-patient relationship and consenting process. "Informed consent" can be defined as: a process of communication between a patient and physician that

results in the patient's authorization or agreement to undergo a specific medical intervention.

There is no medicine that a woman can take to treat POP. And once prolapse reaches Stage II or greater, it is highly unlikely that Kegel exercises will restore her normal anatomy, so the options for this type of patient are expectant management ("living with it"), using a pessary, or having the prolapse surgically repaired. In most cases, surgery offers the best chance of a patient being able to restore her quality of life back to where it was before she developed POP, but as with any surgery, there are risks. These risks include: bleeding, blood clot formation, infection, damage to nearby structures (i.e. bowel, bladder, urethra, ureters, and in some cases the abdominal wall), formation of fistulas (abnormal connections between two organs), shortening of the vagina, difficulty emptying the bowel or bladder afterwards, difficulty controlling her bowel or bladder (i.e. fecal or urinary incontinence and urinary dysfunction), chronic pelvic and/or vaginal pain, pain with intercourse, and in very few cases, death. These risks exist regardless of whether or not a graft or mesh is used in the repair. Transabdominal repairs expose patients to all these risks, as do transvaginal repairs (with the exception of damage to the abdominal wall [i.e. abdominal wound infection and/or hernia formation]).

The only unique risk that exists when meshes are incorporated into POP repair is mesh exposure. Some argue that mesh "contracture" or "shrinkage" is a also a unique risk. It stands to reason that the only way mesh contracture would affect a patient would be with subsequent symptoms: such as shortening of the vagina, pelvic pain, and pain with intercourse - that are listed above as risks for all

POP repairs with or without mesh. That being said, it is clear that mesh exposure is a unique risk that cannot occur if mesh is never placed in the body. Mesh exposure refers to when either the vaginal incision over mesh does not heal properly or mesh wears through the overlying vaginal wall and becomes exposed in the vaginal canal. This risk exists when mesh is used for repair of urinary incontinence or POP, and. it exists whether the mesh is placed transvaginally or transabdominally. This risk has been known for decades (Snyder 1991, Julian 1996). Any patient who undergoes pelvic floor surgery using mesh should be aware that there is a risk of mesh exposure postoperatively.

Prolapse surgeries also carry with them certain benefits. These include the chance to alleviate the symptoms of prolapse. They no longer feel that they are "sitting on a ball" and the constant sense of pelvic pressure goes away. Unlike a pessary, once surgery has taken place these benefits are not dependent on regular office visits. Patients who choose to treat their POP with a pessary usually require visits to the doctor's office every three months for the rest of their lives. They often have to deal with vaginal discharge from the pessary that can be malodorous. They also have to remove the pessary to have intercourse and therefore whatever discomfort or embarrassment they had from their prolapse with sexual activity persists. Many patients who have surgery for POP resume having intercourse after being abstinent as a result of their prolapse, and some have resolution of discomfort that they had with intercourse related to their prolapse. In many cases, patients who had urinary incontinence or (on the other hand) difficulty emptying their bladder have a resolution of these symptoms after surgery. Many have a greater

sense of confidence and restoration of a normal sense of their body image. A common refrain that a pelvic floor surgeon hears is "you have given me my life back."

As with all reconstructive surgery, the reconstructed structures can "fall apart" again. No orthopedic surgeon can guarantee that a knee replacement is 100% guaranteed to last the rest of a patient's life. And no pelvic reconstructive surgeon can guarantee a 100% life-long success rate for his or her prolapse repairs. How long a repair can be expected to last depends on many factors. Potential factors include: how severe the POP is and whether it involves the top, front, and/or back wall of the vagina, how active the patient is, how old the patient is, and patient comorbidities such as diabetes or chronic coughing. As a result, just as all patients getting mesh repairs must be counseled regarding the risk of mesh exposure, all patients getting any type of POP repair must be counseled regarding the risk of recurrent POP postoperatively. The reason most pelvic surgeons include mesh-based repairs (whether it be trans-abdominal or –vaginal surgery) as a surgical option, is to decrease the chance of recurrence. One key to the informed consent process in mesh-based POP repair surgery is that patients understand that they are balancing the potential risks of adding mesh to the repair (mesh exposure) with the potential added benefits (decreased recurrence of prolapse).

V. Prolift

Polypropylene meshes have been used in humans for over 50 years to correct connective tissue defects. Some of the earliest data on such use was published in 1958 and supported the use of this material for the repair of incisional

hernias (Usher 1958). By the 1990's the use of synthetic mesh for repair of abdominal wall hernias was becoming very common. Its use was supported by a randomized clinical trial published in the New England Journal of Medicine in 2000 (Luijendijk 2000). This study showed short term recurrence rates of 43% in suture repairs but only 24% in mesh repairs. Long term follow-up (10-year cumulative rate) showed recurrence in 63% of suture repairs and only 32% for mesh repairs (Burger 2004). Gynecologists were also struggling with high recurrence rates (Weber 2001) of their vaginal prolapse (essentially pelvic floor hernia) repairs and wondered if the use of synthetic mesh could, likewise, cut their failure rates in half.

Gynecologists had already achieved great success in treating stress urinary incontinence with the transvaginal placement of synthetic mesh (Ulmsten 1998) – known as the tension-free vaginal tape (or TVT) procedure - and studies during the evolution of that procedure determined that large pore, monofilament, polypropylene mesh was the best material for these sling meshes (Falconer 1996 & 2001). Other synthetic sling materials resulted in high erosion and infection rates (Weinberger 1995 & Kobashi 1999), but these rates were drastically reduced with the use of the TVT monofilament polypropylene mesh; so much so, that this procedure (along with other forms of midurethral synthetic slings) remains the gold-standard for the treatment of stress urinary incontinence to this day (Ward 2009, Ogah 2009, Iglesia 2012). Long-term studies (11.5 years) of the TVT procedure demonstrate no late adverse events of the operation that were not present in these early studies (Olsson 2010).

One of the benefits of the TVT procedure is that rather than anchoring the sling to one isolated spot (i.e. a bone anchor in the back of the pubic bone), the TVT is placed in a "tension-free" manner. What that means is that the mesh is covered in a smooth plastic sheath during placement which allows the sling to slide easily through the patient's tissues, but once proper placement is confirmed the smooth sheath is removed, exposing the sling mesh to the patient's tissue. The "nooks and crannies" of the mesh then interact with the patient's tissue in a Velcro-like fashion securing it in place, but distributing the load along the whole length of the mesh rather than at a single attachment site.

Given the success of mesh in hernia repair and TVT for stress incontinence, a group of gynecologists in France worked to develop a system for prolapse repair utilizing the transvaginal placement of polypropylene mesh in a tension-free manner. This technique was initially termed TVM (Tension-free or Trans Vaginal Mesh). The first step in determining the ideal system was to choose a mesh material. Macroporous, monofilament polypropylene mesh appeared to be the best option (Cosson 2003). As noted above, this material when used in sling-form to treat UI was proving to be very successful. This material has a very low risk of infection and is suitable for vaginal use. I am aware that plaintiffs' experts claim that the mesh degrades; however, I disagree. I have not seen polypropylene degradation in my clinical practice. In 2002, the USFDA granted clearance to Gynecare to market a macroporous, monofilament polypropylene surgical mesh for the treatment of pelvic floor repair known as Gynemesh PS (Prolene Soft). One year data on the success of utilizing Gynemesh PS for repair of pelvic organ prolapse was

presented at the 2004 Annual Scientific Meeting of the American Urogynecologic Society and demonstrated that it was an acceptable material for the repair of prolapse (Lucente 2004). Complications including mesh exposure were noted in 9.4% of patients, of which 2.5% were managed conservatively, 5% underwent office interventions, and 1.9% were treated in the operating room. Low POP recurrence rates with the use of Gynemesh PS were demonstrated that same year at the combined meeting of the International Continence Society/International Urogynecological Association (Jacquetin 2004). Data on the risks of mesh erosion were also presented at the same meeting (Collinet P 2004). Around this time, the French group was working on developing the TVM technique. The first scientific publication on this work was in 2004 (Debodinance 2004). Data on this technique utilizing this mesh was presented the following year, 2005, at the International Continence Society meeting in Montreal Canada. A low rate of complication was noted. These reported complications included: bladder and rectal injury, vaginal and rectal erosion, intra-operative hemorrhage, post-operative infection, hematoma, and fistula formation. They also noted postoperative mesh shrinkage, granuloma formation, recurrence of POP, and de novo SUI.

TVM initially involved the surgeon cutting a 30 x 30 cm piece of Gynemesh PS along a pre-configured pattern. The bodies of the mesh were placed in the vesico-vaginal space, the rectovaginal space, or both; then arms of mesh attached to the body of the mesh were then brought through supporting structures in the pelvis (arcus tendineous fascia pelvis and sacrospinous ligament) by looping the arms through suture loops that had been placed in a retrograde fashion at the end of

metal trocars. These anatomic compartments and anchoring points had been accessed and used by pelvic surgeons for suture-based repairs for many years previously. A retrospective study of over 600 cases of this technique performed between October 2002 and December 2004 was published in 2008 (Caquant 2008). Long-term results of this technique were published in 2011 (Miller 2011). While this technique produced good results, it was time-consuming to hand-cut the mesh and pulling the mesh arms directly through tissue had the potential to be more disruptive to the tissue than the tension-free tape arms used in incontinence sling surgery.

In an effort to make the TVM technique as efficient and effective as possible, the Prolift system was developed. In the Prolift system, the mesh is pre-cut and the introducing system is significantly improved. The trocar guides are covered by a snugly fit cannula through which retrieval loops can be easily placed. This allows the mesh arms to be brought through the pelvic tissues without touching the surrounding tissues during initial placement. It is only when the system has been placed in the desired final location that the cannulas are removed exposing the mesh arms to the surrounding tissue, thus setting the mesh in a truly tension-free manner – much like removing the plastic sheath from the TVT sling. The system allows tension-free placement without the need for tacking sutures, staples, or other anchoring fixation devices and minimizes the risks of injury.

I am aware that Plaintiffs' experts claim that the design of the Prolift is defective or unsafe. However, I disagree. For example, Dr. Weber claims that Prolift carries unreasonable risk because it involves "blind" passage of trocars. But, much

of surgery is related to palpation rather than visual inspection and surgeons are trained to use palpation during their examination of patients and during surgery. Even with direct visualization, injury to vital structures is possible, i.e. pre-sacral hemorrhage during sacral colpopexy, ureteral injury during hysterectomy. In fact, many steps in vaginal hysterectomy, retropubic pubovaginal sling placement, and the initial steps of laparoscopy involve "blind" surgical steps. All POP surgeries have potential risks. The Prolift system was designed by surgeons to minimize risks while providing adequate and lasting prolapse repair. I also disagree with their claims that Vypro and PVDF would have been better options for the mesh. Vypro was studied by Dr. Jacquetin, a member of the TVM Group, and the mesh was reported to be disappointing. (Jacquetin 2004 ICS) Another study showed a 34% POPQ failure (stage II or greater) at 12 months with Vypro. (Cardozo 2005 ICS). PVDF does not have the clinical data and experience that monofilament polypropylene, and in particular Gynemesh PS, has for tissue reinforcement. Monofilament polypropylene mesh has a long history of use before 2005, was suitable to use in Prolift, and continues to be the most widely used mesh for POP repair, whether vaginally or abdominally, to this day.

I am aware that Plaintiffs' experts also claim that a pore size of 1mm in all directions is needed for reducing the risk of infection, adequate tissue incorporation and proper functioning (what they term as "effective porosity"). However, I disagree and this is nothing more than a theory that is inconsistent with biologic reality, as macrophages, leucocytes, and fibroblasts are all smaller than 50 microns. The mesh in Prolift is macroporous (>75 microns) and allows for proper tissue

integration while reducing the risk of infection. Additionally, the testing performed by Plaintiffs' experts does not reflect what occurs with the mesh in patients and is inconsistent with the forces in the pelvic floor, how the mesh is placed and the use of the cannulas. The mesh is sufficiently flexible provided inserted properly and when deployed properly responds to forces in the pelvic floor and provides support to the prolapse. Overall, the clinical data on the TVM and the Prolift show that the potential benefits outweigh the potential risks.

The first study of the Prolift system to be published in the peer-reviewed literature came out online in November 2006 (Fatton 2007), but abstracts on the Prolift procedure had been presented at scientific meetings prior to this date (Valentim-Lourenco 2006, Murphy 2006). More recently, the results of a large cohort of 524 patients with over three years median follow-up was published and showed a 3% rate of re-operation for prolapse recurrence and a 3.6% rate of mesh-related complications (including 2.5% for mesh exposure and 0.4% for symptomatic mesh contraction) (de Landsheere 2012).

Since 2004, many trials comparing native-tissue repairs to trans-vaginal mesh repairs and even more case series of mesh repairs have been published. These studies include free-cut mesh that is sutured in place directly and other "kit" procedures. A number of notable randomized trials comparing native tissue repairs to mesh procedures other than Prolift can be found in the bibliography (Hiltunen 2007, Sivaslioglu 2008, Nguyen 2008, Nieminen 2008, Carey 2009, and Nieminen 2010). The majority of these studies showed a higher rate of success in treating POP with mesh than with native tissue repair.

Importantly, no other trans-vaginal mesh kit has been studied more than the Prolift system. To my knowledge, the results of five randomized surgical trials comparing Prolift to other techniques of POP repair have been published. Four (Iglesia 2010/Sokol 2012, Withagen 2011, Altman 2011, Halaska 2012) of these trials compared Prolift to native tissue repairs and one (Maher 2011) compared it to a transabdominal mesh repair.

Three of the four trials comparing Prolift to native tissue repairs showed higher success rates with Prolift (Withagen 2011, Altman 2011, Halaska 2012). The other study was halted prior to completion of patient recruitment due to a predetermined stopping criterion (Iglesia 2010/Sokol 2012). This study was halted because a >15% erosion rate of the Prolift mesh was noted before patient recruitment was complete. Despite the small sample size (n=65) and short-term follow-up, greater success was noted in the Prolift arm in regards to correction of the anterior compartment (cystocele repair), as was seen in the other two studies measuring changes in the anterior compartment in which recruitment was completed. One of the three trials that completed recruitment looked at the treatment of recurrent POP in both the anterior and posterior compartments (Withagen 2011) , another (Altman 2011) looked only at prolapse of the anterior vaginal wall (cystocele), and the third looked at apical prolapse in post-hysterectomy patients (Halaska 2012). The study looking at treatment of recurrent prolapse showed less anatomical failures in the Prolift arm in both the anterior and posterior compartments. The study of apical prolapse in post-hysterectomy patients showed fewer anatomic failures and better apical support in the mesh

group. Both of these trials did not show a significant difference in symptoms of recurrent prolapse at one year. They were not designed to detect such a difference, as this was not a primary endpoint of these studies. The only study comparing TVM to native tissue repair that was designed with a composite primary outcome of objective and subjective assessment of vaginal bulging, was the 2011 Altman Prolift study. It is no coincidence that this is also the largest randomized trial comparing TVM to native tissue repair, with 389 patients enrolled from multiple centers. This study published in the New England Journal of Medicine showed higher rates of both objective and subjective success in the Prolift arm. The Prolift arm also had longer operative time, intra-operative hemorrhage and de novo SUI, but only 3.2% of the patients in the Prolift arm needed surgical reintervention for mesh exposure. There were no statistically significant differences in postoperative pain, infection, death, or change in sexual function between the two arms.

Critics of TVM assert that it carries two unique risks with it that do not exist in native tissue repairs: mesh erosion and mesh contraction (shrinkage). These two risks are listed in the 2011 FDA Safety Communication regarding TVM (FDA 2011). This document states that "mesh erosion and contraction may lead to severe pelvic pain, painful sexual intercourse" and that mesh contraction is associated with "vaginal shortening, vaginal tightening and vaginal pain." Notably, mesh erosion and contraction were identified in the first Prolift IFU and data on these and other potential complications were also presented and published. Review of the four RCT's comparing Prolift to native-tissue repairs reveals that these types of outcomes are commonly reported at one year of follow-up. One of the four (Altman 2011)

does not report on changes on shortening of vaginal length and another (Sokol 2012) does not report on pelvic pain. With these exceptions, all four studies report on vaginal shortening, pelvic pain, and pain with intercourse; and none of them report any greater risk of these adverse outcomes with the mesh group. Other descriptive studies (Lowman 2008, Dietz 2011) support these findings and I have co-authored a paper to address some of the shortcomings of the 2011 FDA Safety Communication (Murphy 2011). Over 600 pelvic surgeons endorsed this critique of the FDA Safety Communication.

The other RCT involving Prolift, compared this technique to laparoscopic sacral colpopexy (Maher 2011). These are both mesh-based surgeries, but in the latter the mesh is brought into the body abdominally and sutured to the vagina and the sacral promontory with suture. This study showed higher anatomical success rate with the laparoscopic mesh procedure, but with longer operative times (approximately twice as long). The authors also found a longer hospitalization and return to normal activity with the Prolift procedure, but the values they quote are much longer than those found in most other studies. The laparoscopic surgery also had many concomitant surgeries in addition to the sacral colpopexy. The authors failed to show any difference in symptomatic prolapse between the two groups two years after surgery. Both groups showed significant improvement in symptom severity and quality of life scores, but there were no differences in any of these validated quality of life scores between the two groups. Likewise there was no significant difference in the rate of mesh erosion between the two groups.

This study shows that laparoscopic sacral colpopexy is a comparable procedure to Prolift in many ways, but it was a relatively small sample size (just over 50 patients per arm). This procedure, however, requires considerable laparoscopic skills that are beyond the reach of many urogynecologists and urologists, let alone many general gynecologists. When this procedure is performed with traditional laparoscopy or robotic-assisted laparoscopy it can put patients at risk for certain severe complications that are not seen with transvaginal surgeries such as Prolift. A number of case reports of these types of complications such as lumbosacral osteomyelitis and discitis have been published recently as surgeons strive to perform these more recent minimally-invasive approaches to the sacral colpopexy procedure with the hope that they will provide better results than native tissue repairs (Taylor 2006, Nosseir 2010, Grimes 2012).

While ASC is considered by many to be the "gold standard" procedure for apical repair of POP, a recent Cochrane review (Maher 2010) shows that there are only three published manuscripts of RCT's comparing ASC to traditional native tissue repair (Benson 1996, Lo 1998, Maher 2004). Only one of these trials compared outcomes using validated quality of life instruments to measure subjective outcomes, and no difference in subjective success was noted in this study (Maher 2004). So while many may consider ASC to be the "gold standard" for treating difficult cases of POP; the data to support its use over native tissue repairs is no greater than the data supporting the use of Prolift. In fact, it could be argued that the data in support of Prolift over native tissue repairs is superior to that of ASC. Lastly, many proponents of transabdominal mesh-based repairs suggest that

the morbidity of an open ASC can be mitigated by performing the procedure laparoscopically. However, there are no published manuscripts comparing laparoscopic (traditional or robotic) to open ASC (Maher 2010).

Dr. Weber suggests that Ethicon failed to be responsible by failing to conduct rigorous, long-term clinical studies of the Prolift. This implies that the surgical alternatives to Prolift (those listed by Dr. Weber include: suture-based colporrhaphy, suture fixation, and abdominal sacral colpopexy) were only performed on women after they had been studied with rigorous, long-term clinical studies. Either that or she is implying that physicians who performed these procedures outside of clinical protocols were acting irresponsibly. Likewise she state that the women who received Prolift were unaware that they were "test subjects." Again suggesting that women who received the alternative surgical procedures only did so after rigorous, long-term studies of these procedures had been conducted. These suggestions are dubious and I disagree with them. Moreover, as shown above, Prolift and the transvaginal mesh technique have been well studied and clinical data continues to be generated on its use. My colleagues and I recently presented data on over 1,000 patients receiving Prolift at the 33rd Annual Scientific Meeting of the American Urogynecologic Society in October 2012 in Chicago (Lucente 2012). This study showed a lack of prolapse symptoms in 92.8% of patients at one year after surgery with the Prolift System. Our erosion rate was comparable to that reported in many studies of abdominal sacral colpopexy, 2.9%.

VI. Professional Education/Credentialing

The Prolift system package includes a pamphlet with Instructions For Use (IFU). A Prolift Surgical Technique Guide is also made available to surgeons and is referenced in the IFU. These documents are provided to the users of Prolift as a guide for the use of this particular product. They are not designed to replace sound surgical judgment that pelvic surgeons develop during their training and practice. Nor are they meant to teach the user how to perform pelvic reconstructive surgery. In fact, the 2004 IFU states clearly that, "Users should be familiar with surgical procedures and techniques involving pelvic floor repair and nonabsorbable meshes before employing the GYNECARE PROLIFT Pelvic Floor Repair Systems."

Training was also recommended on Prolift and available; in addition to these tools the manufacturer of Prolift made available to potential users of the product various other forms of guidance for the product including: DVDs of the surgical procedure being performed, animated videos of the relevant 3-dimensional anatomy of the pelvic floor anatomy, and instructional meetings during which didactic lectures were given and the opportunity to perform the procedure on human cadavers was provided. In my opinion, these efforts were more than adequate to prepare a licensed physician trained in female pelvic surgery to perform the procedure.

The IFU also includes a list of potential adverse events associated with the use of the Prolift system in the repair of POP including, "those typically associated with surgically implantable materials, including infection potentiation, inflammation, adhesion formation, fistula formation, erosion, extrusion and scarring

that results in implant contraction." Critics of the Prolift system suggest that by not including "dyspareunia", "pain with intercourse" or "urinary dysfunction," the user of the system would not be aware that these would be potential adverse reactions to a procedure utilizing the Prolift system. This criticism is without base. Any surgeon who performs female pelvic surgery knows that postoperative dyspareunia is a risk with any surgical repair of POP (Nygaard 2004, Lowman (2008). Furthermore, even without this basic knowledge, any reasonable pelvic surgeon could infer that dyspareunia is a risk when the IFU discloses that surgically implanting this material in the vagina can cause inflammation, adhesion formation, erosion, scarring and contraction. Any surgeon who performs female pelvic surgery would also know that postoperative urinary dysfunction is a risk with any surgical repair of POP. The IFU also states "Punctures or lacerations of vessels, nerves, bladder, urethra or bowel may occur during GYNECARE PROLIFT Guide passage and may require surgical repair" and "The GYNECARE PROLIFT Pelvic Floor Repair Systems should be used with care to avoid damage to vessels, nerves, bladder and bowel. Attention to patient anatomy and correct use of the device will minimize risks." It is my opinion that the Prolift IFU was adequate to inform and warn surgeons of the potential risks.

In addition to the above-mentioned written materials, videos, didactic lectures, and cadaver labs, Ethicon made available surgical precepting and proctoring to surgeons who requested these opportunities. Precepting refers to the ability of surgeons interested in the Prolift system to view (in-person) live surgery performed by physicians experienced in Prolift. Proctoring refers to surgeons

experienced in Prolift coming to the operating room of surgeons doing Prolift for the first time to provide in-person guidance.

The American Urogynecologic Society provided written guidelines regarding privileges and credentials for physicians to perform TVM procedures (AUGS's Guidelines Development Committee 2012). The authors of these guidelines suggest among other things that surgeons performing these procedures should "undergo training specific to each device and have experience with reconstructive surgical procedures and a thorough understanding of pelvic anatomy." In addition, they believe surgeons should "read the manufacturer's instructions for use (IFU), observe steps involved in the procedure via animation, video, or live surgery (and) undergo hands on experience with the procedure using simulated models, animal or cadaveric models or other learning models." Ethicon made these materials and experiences available to requesting physicians who wished to perform Prolift even in the absence of this recent guideline. Nowhere in the guidelines does it say that the device manufacturer should be involved with providing privileges or credentialing to perform a procedure such as the Prolift Pelvic Floor Repair System. Providing such privileges falls under the auspices of hospital credentialing committees and department chairmen/chairwomen.

I reserve the right to supplement my opinions as additional information and data become available. I plan to review the testimony of Plaintiffs' experts and reserve the right to respond to it.

Signed: Miles Murphy

Miles Murphy, MD, MSPH, FACOG.

My compensation in this matter is $400 per hour.

In the past four years I have given expert testimony in the following case:

Neff v. Collins in Lycoming County, Pennsylvania in 2009.

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Superior Court of New Jersey
Law Division, Atlantic County

In re Pelvic Mesh/Gynecare Litigation
Case No. 291 CT
Master Case 6341-10

SUPPLEMENTAL ETHICON EXPERT REPORT OF MILES MURPHY, M.D.

I have reviewed the additional Ethicon funded studies, mesh studies to repair POP, and Axel Arnaud's deposition. These studies and testimony further support my opinions in my initial report, including but not limited to those below:

1. Ethicon properly studied and funded studies to support its use of the Gynemesh PS mesh used in Prolift.
2. Multiple studies using polypropylene meshes, including the mesh used in Prolift, were safely and effectively used prior to launch of Prolift to repair pelvic organ prolapse.
3. Ethicon had sufficient studies and trials to support its launch of Prolift.

I reserve the right to amend my opinions pending further discovery.

Executed at North Wales, Pennsylvania on November 28, 2012.

Miles Murphy, M.D.

Updated Materials List

Transcripts

Axel Arnaud deposition transcripts with exhibits
Judi Gauld deposition transcript with exhibits
Michael Margolis deposition transcript with exhibits
Anne Weber deposition transcript with exhibits
Piet Hinoul deposition transcript with exhibits
David Robinson deposition transcript with exhibits
Jessica Shen deposition transcript with exhibits
Vincent Lucente deposition transcript with exhibits
Daniel Elliott deposition transcript with exhibits

Expert Reports

Susan Shott Supplemental Expert Report
Anne Weber Supplemental Expert Reports
Elizabeth Kavaler Expert Reports
Stephen Factor Expert Reports
Laurie Stevens Expert Reports
Roy Filly Expert Reports
Mary Jane Minkin Expert Reports
Jennifer Payne Expert Reports
Daniel Sexton Expert Reports
Larry Sirls Expert Reports
David Williams Expert Reports
Frederick Schoen Expert Reports
William Cobb Expert Reports
Timothy Ulatowski Expert Reports
Daniel Scharfstein Expert Reports

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FDA certified copy of FOIA Request regarding Liscinsky email

Addendum to Miles Murphy, MD MSPH FACOG's
2012 General Report on the Use of Mesh in the Repair of Pelvic Organ Prolapse

Since the time I served my 2012 General Report, I continue to follow the peer-reviewed scientific literature regarding the surgical correction of pelvic organ prolapse. These additional studies that have been published (see "References") further support my opinions from my original report. I continue to hold all opinions to a reasonable degree of medical and scientific certainty. For example, longer term studies on Prolift and Gynemesh PS continue to be published showing that the devices are durable, safe, and effective. High rates of objective/anatomic cure continue to be seen. Consistent with earlier data, patients report significant improvement in prolapse symptoms and quality of life through validated questionnaires after surgery with these devices. They report high levels of patient satisfaction; and in my opinion, the data show acceptable rates of complications when considering the rates of complications for native tissue/non-mesh augmented/suture-based repairs.

RCT's continue to show mesh repairs with the Prolift system continue to show similar rates of adverse events (such as vaginal shortening, pelvic pain, and dyspareunia) to native-tissue repairs as is demonstrated in Table 1 below.

Table 1. Outcomes from one-year follow-up of randomized trials comparing Prolift to native tissue repair procedures for pelvic organ prolapse

	Vaginal Length			**Pelvic Pain**			**Dyspareunia**		
Study	Prolift	Native	P	Prolift	Native	P	Prolift	Native	P
Withagen 2011	9 cm (5-11)	9 cm (4-10)	.22	10.1%	11.8%	.74	17%	23.5%	.41
				De novo 7.5%	**De novo 4.0%**	.44	**De novo 8.1%**	**De novo 10.3%**	.44
Altman 2011	NR	NR	--	0.5%	0.0%	1.0	7.3%	2.0%	.07
							PISQ 35.1	**PISQ 35.0**	.99
Sokol 2012	8 cm (6-10)	8 cm (5-10)	.35	NR	NR	--	6.7%	18.8%	.60
							PISQ 34.0	**PISQ 35.0**	.66
Halaska 2012	7.6 cm	7.3cm	.30	8.1%	5.5%	.73	8.0%	3.7%	.47
							PISQ 33.4	**PISQ 36.5**	NS
Svabik 2014	7.4 cm	7.1 cm	.41	NR	NR	--	5.6%	3.2%	NS
							PISQ 32.6	**PISQ 35.6**	.19
Silveira 2015	NR	NR	--	2.3%	8.6%	.09	3.4%	6.3%	.48
							QS-F 21.8	**QS-F 22.4**	NS

Signed: 

Miles Murphy, MD MSPH FACOG
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